

REPORT OF THE
DIRECTOR OF THE HOSPITAL
OF
THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH

April, 1916.

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To the Board of Scientific Directors
of the Rockefeller Institute.

Gentlemen: -

The Director of the Hospital has the honor to submit the following suggestions in regard to future development of the hospital, and report of scientific work carried on during the past quarter.

NEED FOR INCREASED LABORATORY SPACE : Since its organization, the activities of the hospital have gradually increased, both as regards the number of patients studied and the amount of work carried on by the physicians in the laboratories of the hospital. This increase in activity has made manifest certain limitations in the facilities of the hospital and has made evident that, for further increase, or even for the most advantageous continuation of the work at its present extent, certain changes are advisable. The most evident requirement which has appeared during the past year has been the need for extension of the space devoted to laboratories. The work carried on in the chemical laboratories has increased very materially and as a result, the space originally devoted to this work has been much overcrowded, four and five persons working in a space originally intended for two or three. The bacteriological laboratories have also been much overcrowded. It has been impossible to provide Dr. Allen with proper laboratory space for carrying on his work on diabetes, and he has had to use several single rooms, widely separated.

The Director is of the opinion that in order that those who are engaged in making clinical studies and caring for patients may also carry

on experimental researches relating to the diseases being investigated, it is very important that the laboratories in which these men work shall be in as close proximity to the wards as possible. He drew attention to this matter in his first outline of the proposed organization of the hospital, and his subsequent experience has confirmed this view. Moreover, owing to the advisable limitation in the number of patients, it is important that these patients be studied from different standpoints, that is, that frequently chemical, bacteriological, or biological and physiological studies be carried out simultaneously on the same patients. To make this possible it is important that the men working along different lines work in harmony and in cooperation. If the laboratories are widely separated, this is impossible. For this reason it is better that the men work in somewhat crowded quarters than that they carry on their work in separate buildings, or in laboratories widely separated one from another. It is to be hoped, however, that it may be possible to make some extensions in the space provided for the chemical and bacteriological laboratories. To do this, I have suggested that certain of the rooms now used for bacteriology be equipped for use as an addition to the chemical laboratory, and that temporary changes be made on the west end of the sixth floor to provide for some of the bacteriological work. It is suggested that the changes made on the sixth floor involve as slight structural changes as possible, so that if later it is decided to use this floor for patients, it can be restored to its present condition with comparatively little expense. Sketches of the changes proposed will be presented at the meeting of the Board.

It is expected that Dr. Allen's work for the first part of next year, at least, will consist mainly in experimental work on dogs, and it is there-

fore suggested that suitable arrangements be made for him on the second floor of the present laboratory building, which will be made vacant by the removal of the chemical laboratory to the new building. It is hoped, also, that on this floor an operating room can be provided for Dr. Cohn and also one for other workers in the hospital, whose work may require operative procedures on dogs.

ADDITIONAL ROOM FOR PATIENTS : The growth of the work on cancer will probably increase slightly the number of patients cared for in the hospital. It is hoped that next year it will be possible to care for this slight increase by moderate crowding of the space now available on the 3rd, 4th and 5th floors, and also possibly by using the isolation building for convalescent patients, when necessary.

It is important, however, that at this time the Board consider possible methods for future increase of the number of beds available. The past experience suggests that the need will best be met by providing additional single rooms. In a mixed service as we have, consisting of both men and women, it has been found difficult to separate patients suffering from various diseases without overcrowding certain wards and leaving other wards containing comparatively few patients. Such separation in certain cases seems very important. For instance, certain experiences we have had have indicated that it is very important not to treat pneumonia patients in the wards containing patients with heart disease. It has not been wise to place diabetic patients, who are not acutely ill, and whose mental state is of considerable importance, in wards containing acutely sick pneumonia patients.

It has also been found advisable to keep patients on whom very accurate chemical or metabolic studies are being made in single rooms. Moreover, the demand on the part of persons of the better classes for admission to the hospital has grown, and it is found that in many ways these are the best patients for study, as they are more ready to cooperate in the studies being made. These patients also require separate rooms.

It would seem, then, that the first extension of the hospital facilities should provide for additional single rooms. This can probably best be done by using the second floor, now occupied by nurses, for this purpose. In the original planning and construction of the hospital this floor was built with this possibility in mind, and this floor could be used for this purpose with comparatively slight change.

NURSES HOME : Such a use of this floor would, of course, necessitate making provision for the nurses elsewhere. The nurses quarters are already overcrowded. In very accurate work and complex studies, such as are made in the hospital, the number of nurses required is large, much larger than may be thought necessary by those who have only had experience in the ordinary general hospital. The nurses are needed, not only in caring for the immediate needs of the patients, but they are employed very largely in assisting in making observations and in assisting in the technical procedures carried out. It seems, therefore, that sooner or later a nurses home should be provided. When this is done, provision should probably be made in this building for providing quarters for the doctors, as well. When this is done, the second floor should be available for patients.

REORGANIZATION OF THE X-RAY LABORATORY : It has been well recognized by all those familiar with the work in the hospital that the X-ray work has not been carried out in a manner commensurate with the other

work done. The equipment and service have not been even so good as that of the average general hospital. It is hoped that provision can now be made for greatly improving this service. The work on cancer which it is proposed to do makes such a development very important. Moreover, it is hoped to make certain studies concerning the changes in the size and shape of the heart that will give information as to output of theoretical and practical importance.

To provide space it is proposed to enclose the open space on the eighth floor, and to use all the space on this floor not occupied by the operating suite. Plans of the proposed changes will be presented. Additional equipment will be required, the estimated cost of which will also be presented. It is also hoped that one man can be obtained who will give all his time to this work. With the exception of this man, the changes in the hospital arrangements which will be suggested involve very little change in the size of the staff. The changes will make such future increase possible, but are not for the purpose of providing for any immediate changes. They will relieve the present crowding, and provide proper facilities for carrying on the work as at present planned.

Report of the Scientific Work carried on during the Past Quarter.

ACUTE LOBAR PNEUMONIA : During the present winter (up to April 1st) 70 cases of acute lobar pneumonia have been treated in the hospital. Of these, 14 died, a mortality rate of 20%, which is a distinct lowering of total mortality in a very bad pneumonia year. The cases due to pneumococcus type I were treated with serum, unless they were very slightly ill or were admitted very late in the disease, when serum treatment did not

seem indicated. Of the cases due to type II pneumococci, a few were treated with the extract of serum precipitate. Many of the other cases were treated with optochin. Our purpose is to treat cases of type II with a combination of optochin and serum, or optochin and extract of serum precipitate. It has been important, however, to study first the action of each of these agents alone. The following table gives a summary of the cases and the results as regards mortality.

Cases of Acute Lobar Pneumonia 1915-16 to April 1st.

Type	No. Cases	Mortal- ity	%	Treated Cases.		Untreated Cases	
				No.	Mortal- ity	No.	Mortal- ity
I	22	1	4.5	17	serum 1	5	0
II	23	5	21.7	6	optochin 2	9	3
				5	extract 0		
				3	optochin + extract 0		
III	12	6	50.	6	optochin 3	6	3
IV	<u>13</u>	<u>2</u>	<u>15.4</u>	2	optochin 0	11	2
	70	14	20 %				

The danger of drawing conclusions from mortality statistics in pneumonia must constantly be borne in mind, but as they stand the results seem interesting and instructive.

The results of serum treatment in the type I cases add further evidence for the value of the immune serum in this type of case. Our conclusions as to the value of the serum, however, are based on the study of the cases, rather than on the mortality statistics.

The statistics give little information as to the value of optochin in the treatment of pneumonia. However, the studies of the cases have given us valuable information in regard to the use of the drug. Seventeen cases

have been treated with optochin, 9 of type II, 6 of type III, and 2 of type IV. Of these seventeen cases, twelve have been very carefully studied. These studies have yielded important results as regards the size and spacing of the doses. From these studies it seems that careful attention should be given to the size of the body in deciding the size of dose required. It is now thought that at least .024 gm. per Kg. per 24 hours should be given. In the earlier studies it was thought that in certain cases the drug was not completely absorbed, but it seems now that these apparent differences have been due to insufficient and improper dosage. It is apparently best to give a good sized dose at the beginning and to follow this by small doses frequently repeated. These results have been obtained by making studies of the bactericidal power of the blood very frequently during the period of administration. By this biological test the amount of optochin in the blood at any given time may be estimated. With the exception of the case of amblyopia which was observed earlier in the year, no further bad effects of the drug have been seen. In the case mentioned, recovery was complete.

It is too soon to speak of clinical results in the cases treated with optochin, but the impressions obtained have been very decidedly favorable. The clinical results obtained, together with the experimental evidence, make it important that the study of this drug be continued further. It is hoped that by combining the drug with serum much better results can be obtained in cases of type II and type III than with either serum or optochin alone.

Studies have been made by Dr. Moore concerning the acquirement by bacteria of "fastness" to optochin. This is undoubtedly an important question in relation to treatment. The very interesting observation has been made that when pneumococci are grown in serum to which optochin has been added,

either by administration during life or addition in vitro, the pneumococci acquire very large capsules, much larger than those seen when the bacteria are grown in serum alone. By repeated transfers in optochin-containing medium, the bacteria are able to grow in very much higher concentration of the drug than was originally the case. After only a few transfers slight powers of resistance become evident, but several weeks or months are required before the changes become of extreme grade. It is of interest that when the organisms become very resistant to optochin, they also become bile insoluble.

The supply of optochin in this country is very limited, but permission has now been obtained from the German government for a small amount to be exported and also from the English government to allow it to come through, so it is hoped that we shall now soon have enough for our purposes.

Dr. Chickering is continuing his study of dissolved precipitate. In his work with Dr. Gay last summer observations were made which suggested that such precipitates acted not only by supplying immune bodies, but also stimulated leucocytosis and caused mobilization of the normal antibodies. The present studies are being made to determine whether or not the pneumococcus precipitates have any such action. The work has not yet progressed far enough to permit conclusions to be drawn.

Pneumococcus mucosus - Type III. As previously mentioned, pneumococci of this type have been very frequently found in normal mouths. On the other hand, pneumococci of types I and II are never found in normal mouths except in the case of contacts. Since the pneumonia caused by pneumococcus mucosus is relatively infrequent and is of very great severity, these results with pneumococcus mucosus are very surprising and make difficult the interpretation which has been placed on the findings of type I and

II as relates to epidemiology. It is conceivable, however, that the pneumococci of type III found in normal mouths differ in some way from the pneumococci of type III found in disease.

To test whether immunological differences could be found, Dr. Avery has collected about 70 strains of this type of organism from normal mouths, and from patients with pneumonia. He has studied with much care, but no cultural or other differences could be detected. Rabbits were immunized to various strains and cross reactions with the various strains studied. The results, however, were negative; no differences between the strains could be made out.

It will be recalled that in our earlier studies of this organism it was never possible to obtain an immune serum which would agglutinate these organisms unless the latter were first treated with acid to remove the capsules. In our work rabbits, sheep and goats were used in the attempt to produce an immune serum, but on account of the results obtained, horses were never employed. The immune serum from smaller animals had slight protective power for rats, but it had absolutely no effect when tested with mice.

The State Board of Health under Dr. Wadsworth's direction, however, proceeded to immunize a horse, and after several months immunization sent us some serum for testing. To our great surprise it was found that this serum had well marked agglutinating power for pneumococci of type III, and also some protective power for mice, 0.2.cc. serum protecting against doses as high as 0.001 cc of culture. The agglutination reaction is very short and complete in low dilutions, but does not occur in high dilutions. The degree of protective power does not suggest that the serum can be of much effect

in treatment, but the demonstration has been made that an immune serum can be obtained from horses and it is not impossible that methods may be found for increasing its potency. This serum was tested by Dr. Avery against all of the strains which he had collected, and was found to be active against all but 3 of them. These 3 strains were non-virulent and were from normal mouths. However, it was active against other non-virulent strains from normal mouths, so that it has not been possible by this serum to distinguish between the parasitic and non-parasitic strains. In general, the strains from normal mouths are less virulent for mice than are the strains from cases with pneumonia, but this is not constant. The frequent occurrence of pneumococcus mucosus in normal mouths, therefore, is still obscure. Further studies are being made on this problem. The immune serum had no effect on four strains of cocci with large capsules and forming mucous, which, however, were bile insoluble, were haemolytic and did not ferment inulin, and have therefore been called streptococcus mucosus. The serum, therefore, offers a ready means of distinguishing between Pneumococcus mucosus and Streptococcus mucosus.

Dr. Avery has also studied the effect of growing pneumococci in dilute solutions of bile. It has been found that by prolonged growth in this medium, gradually increasing the concentration of bile, the bacteria become accustomed to concentrations of bile, which with the untreated strains cause immediate solution. This property, however, is lost after one or two transfers on non-bile containing medium.

Epidemiology. Dr. Ernest Stillman has, during the past winter, made a study of the types of pneumococci present in the mouths of a large number of normal persons, contacts and convalescents. This material, in

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addition to that already obtained by Dr. Dochez and Avery, gives considerable information in regard to epidemiology, though there are still many obscure questions. Dr. Stillman has studied 270 specimens of sputum from 246 normal mouths. In 132, or about 50% of the instances, pneumococci were present. There has been no difference found in the percentage of persons harboring pneumococcus as studied in the different mouths. This study, however, has been entirely carried out during the so-called pneumonia mouths. Continuation of the study through the summer may show differences. In 2 instances the pneumococci found were of type I, 4 type II, 14 atypical II's (a,b, or x), 29 type III and 83 type IV. In all cases but one in which type I or II were found, the persons harboring them were closely associated with persons suffering from the disease. The epidemiological significance of the carriers of atypical type II and of type III is more obscure. It seems that in this respect the organisms more closely resemble the type IV pneumococci. The extreme virulence of the organisms of type III, however, makes this difficult to understand. In this connection a surprising observation has been made. Pneumococci of type III very quickly disappear from the mouth and sputum after an attack of pneumonia due to this organism. On the other hand, they may persist for months and even years in normal mouths.

It is hoped and expected that other interesting and valuable information will be obtained from this statistical data after the work has been completed.

Production of Immune Serum. The two most important practical points to be solved in the study of immune serum are improvements in the methods of producing serum so as to produce a more active serum and, second, methods of determining proper dosage.

Considerable work has already been done on the first of these problems. Last year the study of immunization of rabbits showed that better results could be obtained by the use of small doses of dead organisms, frequently repeated, than could be obtained by living cultures. This method has now been applied in two horses, one being immunized to type I pneumococcus, one to type II. In both cases, after immunization over a period of 6 to 8 weeks by the method mentioned, sera have been obtained which are as active both as regards agglutination and protective power as any serum we have previously had, using other methods. Attempts are now being made to drive the immunity higher in these horses by employing living cultures, according to the method used by Dr. Flexner and Dr. Amoss. It is hoped that in this way the effectiveness of the serum can be increased, but in any case a method for economizing time and horses has been secured.

Dr. Avery has also conducted some experiments to study the haemolytic action of pneumococci in the hope of using this reaction as a delicate test for immune bodies. The experiments bearing on this problem are not yet far enough advanced to report, but he has brought confirmation of the conclusions drawn from our previous studies, that the haemolytic action is due to substances contained in the bacterial cells, and set free on their solution. Dr. Chesney's studies enabled him to test the haemolytic effect of cultures at various stages of growth. The cultures began to have haemolytic power only at a period when Dr. Chesney was able to show that dissolution of part of the organisms in the culture was occurring. This haemolytic power persists for four or five days, then gradually disappears and after eight days is entirely absent.

Dr. Chesney has continued his studies concerning rate of growth of pneumococci. By means of observations carried out on the supernatant

fluids obtained by centrifuging portions of a culture at varying intervals during the period of maximum rate of growth, it has been demonstrated that toward the end of the period of rapid growth substances or factors are present which bring about the death of a large proportion of the pneumococci, which substances remain in the supernatant fluid after centrifugalization. It has further been shown that the process of destruction or killing of the pneumococci follows or is identical in its rate with that of a so-called monomolecular reaction of physical-chemistry, and in this respect the effect of the fluid constituents of the media upon the bacteria is analogous to the effect (observed by other workers) of bactericidal agents such as phenol and bichloride of mercury upon anthrax spores and upon cultures of bacillus paratyphosus. Furthermore, some evidence has been accumulated to show that these bactericidal substances in the culture medium disappear in part when the culture is allowed to stand in the incubator for several days, for a filtrate obtained from a culture at the end of 24 hours incubation shows decidedly more bactericidal activity for actively growing pneumococci than a filtrate from the same culture 48 hours old, and at the end of 6 days incubation, when there are no longer any living pneumococci present in the culture, the filtrate from that culture shows decidedly less bactericidal action for actively growing pneumococci introduced into it than did either the 24 hour filtrate or the 48 hour filtrate.

It has been possible to cause pneumococci to grow less rapidly by exposing them to the action of filtrate or supernatant fluid obtained from 24 hour broth cultures of the same strain, if, after exposure to such an environment at ice-box temperatures, the pneumococci be removed and reinoculated into unused broth. Attempts have been made to follow the behavior of pneumococci from actively growing cultures (during the period of maximum

rate of growth) when injected into rabbits intravenously, and to contrast, under these conditions, the behavior of these actively growing pneumococci with the behavior of pneumococci which would show a definite lag in the test tube. The study is not complete, but the preliminary experiments suggest that perhaps there may be a difference in the behavior of "young" and "old" cultures of the same strain of pneumococcus, when they are injected intravenously into rabbits, the individuals from a culture during the period of maximum rate of growth tending to increase in number in the blood stream of the rabbit somewhat more rapidly during the period immediately following injection than do the individuals from a culture which is no longer growing rapidly. It is proposed to carry out this study at greater length.

Dr. Dochez has continued his studies relating to the enzymotic activity of pneumococci. In a previous report it was shown that antipneumococcus serum possess the capacity to inhibit the growth of pneumococcus in vitro. After this phenomenon had been definitely confirmed, an explanation of its mechanism was sought. In the course of the investigation it developed that antipneumococcus serum has the capacity to inhibit more or less completely the peptolytic and glycolytic functions of the pneumococcus. From this it has been assumed that inhibition of growth is in part at least dependent upon the antienzymotic properties of immune serum. This quality of inhibition of metabolic function is possessed in varying degree by the sera of normal animals and may have some relationship to their natural resistance. Human sera during lobar pneumonia exhibit the capacity of inhibition, and the degree of inhibition reaches its maximum grade during the period of recovery from the disease. It is thought that for the animal body to rid itself of infection the growth of the infecting microorganism must first be arrested, and that only after this has occurred

do the more specific substances have an opportunity to exert their full effect.

An attempt has been made by use of the methods previously described to throw some light upon the phenomenon of parasitism. It is obvious that, in order for a microorganism to develop a parasitic phase, it must be able to grow in the animal body, which implies the development of a mechanism for resistance to the antigrowth influences of animal sera. A study of the pneumococcus shows that the metabolic functions of organisms recently isolated from the human body are more resistant to the inhibiting factors of both normal and immune sera than are those of organisms which have led a saprophytic existence for considerable periods of time .

A study has also been made of the nature of the antienzymotic substances of the immune sera. It has been possible to obtain specific immune bodies in a fraction of the serum which does not exhibit antienzymotic activity, but no light has been shed, so far, upon the actual nature of the substances themselves, or upon their source. They are thought to be non-specific in character, and their efficiency is believed to be markedly enhanced by the presence of specific immune bodies. Up to the present time, work has been carried on entirely with living organisms, a difficult procedure in work of this kind because of the low virility on artificial cultivation of pneumococci recently removed from a parasitic state. For example, it takes some weeks for a strain of pneumococcus recently isolated from the human body to acquire a capacity of uniform growth on artificial media. A considerable simplification, however, has recently been made in the fact that a peptolytic ferment has been prepared which is active in the absence of the living cell. This method should render the interpretation of comparative experiments much more reliable.

DIABETES, Dr. Allen : The principal effort is now being directed toward publication of the data at hand. The work still in progress centers around the acidosis problem. All diabetic patients are now cared for by Dr. Fitz. Practically no patients are admitted except those with marked acidosis, and Dr. Fitz is studying especially the concentration of acetone bodies in the blood and urine. There are two current theories of diabetic intoxication; one, that it is a pure acidosis; the other, that it is a specific poisoning with acetone bodies. Acidosis is being measured by the carbon dioxide of the blood and alveolar air, and by the total acidity of the urine. The concentration of acetone bodies is being determined by a modification of Marriott's micro-method. Obviously the typical patient approaching coma shows high acidosis with high concentration of acetone bodies, but in special cases it may perhaps be possible to separate the two factors and learn whether one or both may be chiefly responsible for the entire condition or for individual symptoms, or whether there may possibly be another factor, viz., intoxication by yet unknown intermediary products, especially those arising during fat metabolism. As is known, the treatment employed in this hospital aims especially to prevent this intoxication and to remove it when present by means of fasting and suitable diet, rather than to attempt to neutralize it. But in patients bordering on coma, the question of alkali therapy inevitably presents itself, and evidence is accumulating that intelligent use of sodium bicarbonate is beneficial at a certain stage in some cases. The doses used are, however, relatively small, and the alkali is employed as a temporary adjuvant, and not as the principal treatment.

It is believed that the reproduction of human diabetes in experimental animals, and the experimental foundation of the fasting treatment, are now

fairly complete, with the exception of the feature of acidosis. A few animals have been caused to develop what appears to be the same fatal intoxication found in human diabetes. Hitherto no satisfactory reproduction of diabetic acidosis in animals has been achieved, and the present study is therefore believed to be important, to complete the experimental counterpart of the clinical disease, and also to afford a basis for a more fundamental study of the condition than is possible in human patients.

Five patients of this Hospital have been studied in the Russel Sage Calorimeter, under Dr. Eugene Du Bois and staff. From the same standpoint, a few diabetics from other hospitals have also been studied by Dr. Du Bois. A paper (Allen & Du Bois) now in press embodied the results with all the Rockefeller Hospital patients except one. The results are essentially as follows: (1) The existence of the Lusk dextrose-nitrogen ratio of 3.65 : 1 in certain cases is confirmed, but this is not necessarily a "fatal" ratio and such patients may recover considerable tolerance. (2) The respiratory quotient under these circumstances is about 0.69. All the severe cases showed very low quotients, indicating that they were actually of greater severity than most cases called "severe" in the literature. (3) The metabolism of severe diabetics is increased when compared on an accurate basis with that of similarly emaciated non-diabetics, or when the same patient with active diabetes is compared with himself when free from active symptoms. These results are believed to be important in this disputed field. (4) The metabolism is greatly reduced by the fasting treatment. One patient showed a fall of 25% in the basal metabolism during the initial fast. The lowest metabolism observed in these patients is 36% below normal. (5) The respiratory quotients prove that restoration of the carbohydrate-burning function occurs under the fasting treatment. (6) Respiratory quotients have been

found quite frequently which are puzzling, because higher than can be accounted for by known facts.

CHEMICAL LABORATORY, Dr. Van Slyke: With Mr. Cullen and Dr. McLean, work on the fate of protein digestion products is being continued. Up to the present, it has been shown that amino acids increase in the blood during digestion, but that the intermediate compounds, or peptones, do not. The study is now being extended to discover the effect of digestion on the proteins of the blood plasma.

It was found desirable to improve the methods for quantitative determination of the fibrin, globulins, and albumin in the plasma, and Mr. Cullen has succeeded in making these methods sufficiently accurate and convenient to permit their use in experimentation on a considerable scale. The fibrin is precipitated from the oxalate plasma by addition of calcium chloride under definite conditions, and is determined by Kjeldahl. The albumins and globulins are separated by the usual ammonium sulfate method. The difficulty here was to find a satisfactory means of removing the ammonia in order that the nitrogen of the proteins might be determined. Boiling with even dilute alkali decomposes the proteins. It was finally found that if magnesium oxide were used as alkali and alcohol added in ascertained proportions, the ammonia could be boiled off completely in 20 minutes without decomposing the proteins.

Miss Vinograd has been engaged in a study of the proteins of human milk compared with those of cows' milk, the distribution of the nitrogen among the various types of amino acids being determined by methods worked out previously in our laboratories. The problem was suggested by Dr. Holt because of its interest from the pediatricist's standpoint. The results indicate that the albumins from the two milks are of definitely different

amino acid composition, but no difference could be determined in the caseins.

Miss Vinograd, cooperating with Dr. Losee of the Lying-In Hospital, has studied the distribution between maternal and placental bloods of salvarsan injected into pregnant syphilitic women before delivery. The arsenic content of the placental blood one and two hours after the injection was much less than that of the maternal, and, in some cases, was nil. From the results obtained, it appears, therefore, that relatively little of the salvarsan passes the placenta and reaches the foetus. The arsenic determinations were done by methods previously devised by Miss Vinograd for use in Dr. Swift's salvarsan work.

Dr. Palmer, in examining urines of pneumonia patients, has noted in severe cases the presence of considerable amounts of an apparently unknown organic acid. He is at present endeavoring to isolate and identify this.

He is also engaged in perfecting a method, preliminary work on which had been done at the Babies Hospital, for determination of the total organic acids in the urine after precipitation of all the mineral acids, except H Cl, by means of barium hydrate.

Drs. Stillman and Fitz are continuing the study of the blood, alveolar air, and urine in diabetic acidosis. The relationships of other factors to the bicarbonate content of the blood plasma have been studied, with the following results.

Patients with B-oxybutyrate in the blood show a lowering of the bicarbonate below normal to almost exactly the extent that is calculated on the assumption that the B-oxybutyric acid displaces its chemical equivalent of bicarbonate. This relationship is temporarily lost after administration of sodium bicarbonate, which may restore the blood bicarbonate to normal, and relieve the symptoms of acidosis without causing the disappearance of the B-oxybutyrate from the blood.

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The alveolar carbon dioxide is not so reliable an indicator of the actual alkaline reserve of the blood in diabetics, at least when undergoing fasting, as it is in normal individuals. A number of the diabetics under observation show habitually an alveolar CO_2 tension 25 to 40 points below normal when the plasma bicarbonate is normal and there are no symptoms of acidosis. In such patients the respiratory center appears to be abnormally sensitive.

For the past year we have been attempting to find a numerical factor for the acid excretion in the urine which would bear some definite relationship to the actual alkaline reserve of the blood. The ordinary figures of ammonia excretion per day, etc., vary so irregularly when compared with

blood conditions that the existence of any definite relationship between blood and urine seemed doubtful. It now appears, however, that the Ambard formula, here frankly empirical, does indicate a relationship. Indicating the daily excretion of ammonia + titratable acid, in terms of cc. of N/10, by D , the excretion per liter by C , and the body weight by W , the formula $\frac{D}{W C}$ gives a value which varies indirectly as the blood bicarbonate, i.e., it is nearly zero when the percent of CO_2 , bound by plasma is at its maximum of 80; it is about 25 when the plasma CO_2 is 55, both figures expressing the extremes of normal limits on the border of acidosis; and it is about 50 when the plasma CO_2 , also changing by 25, falls to 30 per cent, the point at which acidosis becomes critical. Like the alveolar CO_2 , the urinary excretion is only an indirect measure of blood conditions, and depends upon the normal function of an entire excretory mechanism, so that urine analysis can not be so accurate an index of internal conditions as analysis of the blood itself. But the relationship of acid excretion to internal alkaline reserve appears now so much more definite that a new significance and value can be attached to the excretion figures.

A study of the effect of bicarbonate administration on the alkaline reserve has yielded results of interest. The bicarbonate is not retained in the blood, but appears to be immediately distributed to all the body fluids. The rise in plasma bicarbonate following administration per os or intravenously is approximately the rise that would be expected as the result of adding the bicarbonate to a solution equal in volume to all the water in the body, estimating the latter at 0.7 of the body weight. This fact is of assistance in calculating the effect of a given dose of bicarbonate. Roughly stated, for an individual of 40 Kg. weight each gram of bicarbonate raises the plasma $C O_2$ about 1 volume percent.

A systematic study of the therapeutic use of bicarbonate in acidosis is being taken up by Drs. Stillman and Fitz, and thus far the claims of Magnus-Levy for the indispensibility of alkali therapy in critical acidosis appear to be substantiated. By studying simultaneously the plasma bicarbonate and acid excretion it is hoped that the use of alkali therapy may be put on a more exact basis.

Mr. Cullen is cooperating with Dr. Chesney in a study of the development of acidity during the growth of pneumococci and the influence of the reaction of the medium on growth.

NEPHRITIS, Dr. McLean: The study of the mechanism of urea excretion and urea retention by means of the numerical laws governing the rate of excretion of urea is being continued in patients with disturbed function due to nephritis, or secondary to disturbed circulation in heart failure. In over 1000 observations made these laws have been found to be valid and to give the maximum of information regarding the particular function of the kidney which has to do with the excretion of urea. It has been possible to follow the changes in function during recovery from acute nephritis and the downward tendency preceding uraemia. It has been found that the so called

"retention" of urea in the blood is, in fact, a compensatory mechanism, in order to provide the condition necessary for its excretion through a damaged outlet.

Study of the chlorid metabolism is also being continued in a similar way. This work has presented some interesting and complicated problems. A sudden fall in the concentration of sodium chlorid in the blood plasma has been observed in patients shortly before death from uraemia, the concentration of chlorid in the plasma previously being high. This fall has been shown to be due to an increase in the H ion concentration in the blood, which causes chlorid to increase in the cells and to diminish in the plasma, as had previously been shown by Hamburger, both in experiments in vivo and in vitro.

We are attempting to explain certain fluctuations in the concentration of sodium chlorid in the plasma, previously described, but not understood, such as the lowered concentration of chlorids in the plasma in pneumonia, and in diabetes. Experimental work is being carried out with Dr. Van Slyke to test the effect of the introduction of salts, acids, bases and non-electrolytes into the circulation on the chlorid content of the plasma, and it has been found, both in man and dogs, that introduction of certain other salts into the blood by mouth or intravenously causes a diminution of the chlorid content, apparently by replacing the chlorids by other salts. These questions are being investigated particularly with reference to the mechanism and inter-relationship of salt retention and edema.

With Dr. Cohn the effect of various diuretic drugs, especially digitalis, diuretin and theocin, on the specific ability of the kidneys to excrete water, urea and salt is being studied.

The influence of dietetic therapy in nephritis, on the various functions of the kidneys, and on edema, blood pressure, and other symptoms, is being carried out on the patients under observation. So far we have not observed any direct relationship between diet, especially with regard to its nitrogen content, and the systolic or diastolic blood pressure,

HEART-DISEASE, Dr. Cohn: Early in February, Dr. Jamieson left the hospital to join the Canadian Military Medical Force for service, and since then the work in heart disease has been carried on by Dr. Cohn alone.

The study of the action of digitalis in patients in pursuance of the plan formed some time ago has been continued. The study of the action of digitalis in patients with pneumonia has, in part, been completed and reported. The results have shown, first that digitalis is active in patients with fever, and second, that it may be of benefit in certain cases of pneumonia.

The question of the best way to give digitalis in pneumonia has also received attention - for two reasons especially. First it is important to be able to subject pneumonia patients to its influence as rapidly as possible; second, it has been suggested that if the total amount of the preparation of known strength calculated for a patient of a given weight be given at once, time will be saved and more accurate dosage instituted, and simplification in administration accomplished. We have thought it important to test this second point, and have accordingly treated pneumonia patients with appropriate doses, given in a short period of time, and in certain patients are comparing both concentrated and fractional methods of administration. We have arrived at no definite conclusion as yet, but so far it appears that, in studying the question of administration the rate of excretion of the drug, the optimum concentration in the circulation (after absorption), and the attainment of its threshold value in the heart muscles must be considered.

It seems that by a rapid concentrated administration of the drug, the heart muscle may not be exposed a sufficiently long time, and the threshold value may not be reached before excretion of considerable amounts takes place. The object of single large doses may therefore be defeated.

Experiments are being made on the subject of general and special cardiac hypertrophy. The plan of these experiments has been reported before. To produce general hypertrophy we are running dogs on a tread mill two or three hours a day. The effect on their hearts is being controlled by X-rays and by the electrocardiogram. The post mortem findings are to be analyzed and compared. Special hypertrophy we hope to see result from the experimental injury of aortic and mitral valves. The results of these injuries are to be studied in the same way as those occurring in running dogs.

Earlier experiments on stimulus production in the auricles, and on the vagal and accelerator control of the sinus area have already been reported. The anatomical work is nearing completion and will be reported later.

Certain clinical studies of more than usual interest have been made. First, two instances of vasomotor angina pectoria (Nothnagel) in the case of young men having marked aortic insufficiency have been studied. Both patients suffer from repeated daily attacks. In the case of both the occurrence of such daily attacks is interrupted by the development of febrile attacks of a few days duration, accompanied by abdominal pain. In one case the febrile period occurs with surprising regularity every two weeks, lasts 4 - 5 days, is accompanied by a leucocytosis (20000) , with a relative increase in the polymorphonuclear leucocytes. A cause for the recurring febrile attacks has not been found. The total cessation of anginal attacks during the febrile period is also not explained.

Second, a child has been observed during two attacks of acute rheumatic fever with an interval of a year. During the interval the tonsils have been removed. In the first attack a green forming streptococcus was isolated from the blood by Dr. Swift. In the second attack, a similar organism has been isolated and has been given to Dr. Swift for study. He reports that the immunological reactions which he was fortunately able to make (since he had preserved the original culture and also the serum of animals immunized to it) failed to show the identity of the two organisms.

Finally, we were able to observe rapid heart action (ventricular rate 230 - 240) in a child of 12 over two long periods, about 8 and 36 hours. The rapid action could be terminated by left ocular pressure only. The paroxysms of tachycardia were auricular in origin and probably depended for their formation on a site at a low level in the auricular muscle. In intervening periods, the competition for dominance in stimulus production between this site and the usual one can apparently be observed. The heart of this child is enlarged; the valves are apparently normal. There was no fever. There is a history of vague transient cervical glandular involvement. A progressing myocardial lesion seems to be the probable cause of the irregularity and the hypertrophy.

CANCER: This work is being carried on under the direction of Dr. Murphy. Dr. Montgomery came to the hospital in the middle of February to care for the patients suffering from cancer, and since then three such patients have been admitted and are being studied. Several more are now waiting to recover from operations in other hospitals before admission. It has so far not been necessary to open the special ward on the sixth floor to care for these patients and, as the number of patients with pneumonia will soon begin to diminish, the present available beds will probably be sufficient until next autumn.

The present purpose of the study is to ascertain whether by small doses of X-ray the same response on the part of the lymphocytes can be obtained in man as had already been observed in animals. In the second place, if this lymphocytosis can be brought about, to observe what effect this may have on an individual's resistance to cancer. Patients who have had incomplete surgical removal of cancer, preferably cancer of the breast, have been selected for study. It is hoped to obtain cases as soon as possible after operation. Two cases have now been under observation over a month. The first was a breast carcinoma with the extensive involvement of the axilla. As the new growth had invaded the large vessels, it was impossible to remove it completely. Treatment was started here about three weeks after operation. This consisted of a small general exposure to X-ray of the whole body, with the exception of the involved area. The second case was one which had had the right breast removed for cancer five years ago, and the left breast removed about one month ago, for a very extensive growth. This woman received practically the same treatment as the first one, and both have reacted in practically the same fashion to the treatment. There was a slight fall in the circulating lymphocytes, both in percentage and

in actual numbers, which reached its lowest level 48 hours after treatment. This was followed by a percent rise which in one case went to 52%, and in another to 32%. In both cases there was a secondary fall after about one week, followed by a second rise, which in both cases went higher than the initial one. In the first case this went to 56% and in the second to 50%. The increase in actual numbers of lymphocytes in the first case was, at its highest, 50% above the initial level, and in the second case was 100%. Both cases now after about 1 1/2 month still retain a fairly high level, but with a tendency to sag. A second course of treatment is being given at the present time. A third case of much the same type is under treatment, but it has not been followed long enough to make a report on it at present.

In addition the blood counts of two cases at the Vanderbilt Clinic which are being treated with the destructive dose method of X-ray are being followed, in order to determine how much of a general effect these local applications of X-ray have.

In addition to the clinical work, attempts are being made to determine the X-ray dosage which is required to kill the cancer cell, using for this purpose transplantable mouse tumors. This is being estimated in terms of the possible dose to man.

The experiments so far have demonstrated that exposure to a dose 50% above that which the human skin can stand has no appreciable effect on the growth of these tumors when returned to the animal. These experiments are being continued with both filtered and unfiltered rays. The machine and tubes have been standardized by Dr. Wetherbee, and it is now possible to continue the work along more scientific lines.